

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 04 JUL 2006

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| Applicant's or agent's file reference CJG/PB60780 | | FOR FURTHER ACTION | | See Form PCT/PEA/416 |
| International application No. PCT/GB2005/000939 | | International filing date (day/month/year) 10.03.2005 | Priority date (day/month/year) 12.03.2004 | |
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| Applicant GLAXO GROUP LIMITED | | | | |
| <p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> | | | | |
| <p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p> | | | | |
| Date of submission of the demand 16.08.2005 | | Date of completion of this report 03.07.2006 | | |
| Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016 | | Authorized officer Seitner, I Telephone No. +31 70 340-2389 | | |



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/GB2005/000939

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-75 as originally filed

Claims, Numbers

1-9 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 7 (with respect to industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 7 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*).
- ☐ no international search report has been established for the said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
 - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|---------|
| Novelty (N) | Yes: Claims | 2-9 |
| | No: Claims | 1 |
| Inventive step (IS) | Yes: Claims | 2-9 |
| | No: Claims | 1 |
| Industrial applicability (IA) | Yes: Claims | 1-6,8-9 |
| | No: Claims | |

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 7 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 96/05194 A (DR. KARL THOMAE GMBH) 22 February 1996 (1996-02-22)

D2: EP-A-0 612 741 (DR. KARL THOMAE GMBH) 31 August 1994 (1994-08-31)

D3: WO 2004/018432 A (ELI LILLY AND COMPANY; GADSKI, ROBERT, ALAN; HIPSKIND, PHILIP, ARTHUR;) 4 March 2004 (2004-03-04)

V.1. Novelty:

Documents D1 and D2 disclose compounds (see in D1: page 76, compound (9), page 93, example 10; in D2: page 45, examples (29) and (31)) falling within the scope of the present general formula (I).

Applicant argues that the group R^2 cannot be substituted by a carboxylic or ester group.

However, according to claim 1, R^2 may be substituted by $-C_{1-6}alkyl-COR^5$ with R^5 being hydroxy or $C_{1-6}alkoxy$ (see page 76, lines 26-27 and 36).

Thus, the compounds of D1 and D2 correspond to present formula (I) of claim 1, when $R^2 = -heterocyclyl-X-C_{3-8}cycloalkyl$ with X being a bond, the heterocyclyl of R^2 being

substituted by =O and the cycloalkyl of R² being substituted by -C₁₋₆alkyl-COR⁵ (with R⁵=hydroxy or C₁₋₆alkoxy).

Therefore, the subject-matter of claim 1 is not novel over the prior art (Article 33(2) PCT).

The compounds of claim 2 and the pharmaceutical use of compounds of formula (I) for the treatment of neurological disorders have not been disclosed in the prior art.

Therefore, the subject-matter of claims 2-9 is novel (Article 33(2) PCT).

V.2. Inventive Step:

The subject-matter of claims 1-9, in as far as novel, is considered as involving an inventive step in the sense of Article 33(3) PCT:

Document D3 is regarded as being the closest prior art the subject-matter of the present application and discloses (see page 39: example 32; page 37: example 20; page 1; claims 9-15) benzazepine derivatives which are histamine receptor antagonists for the treatment of Alzheimer disease, mood and attention adjustments, cognitive deficiencies, obesity, dizziness, schizophrenia, epilepsy, sleeping disorders, narcolepsy and motion sickness.

The general formula (I) of claim 1 differs from these known compounds in that the nitrogen atom of the benzazepine ring is substituted by cycloalkyl (corresponding to the definition of R₁) and the phenyl ring of the benzazepine ring is substituted by aryl, heterocyclyl, heteroaryl (corresponding to the definition of R₂). In the compounds of D3 the nitrogen atom is substituted by cycloalkyl-methyl and the phenyl ring by piperidinyl-alkoxy.

The problem to be solved by the present invention may therefore be regarded as the provision of further histamine receptor antagonists for the treatment of neurological disorders.

In view of the teaching of the prior art, the skilled person had no incentive to undertake above mentioned modifications on the compounds known from D3 when searching for further histamine receptor antagonists for the treatment of neurological disorders.

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Hence, the novel subject-matter of claim 1 and the subject-matter of claims 2-9 is considered as involving an inventive step (Article 33(3) PCT).

V.3. Industrial Applicability:

The present application relates to compounds which are useful for the treatment of neurological diseases and the subject matter of claims 1-6 and 8-9 is therefore considered as industrially applicable (Article 33(4) PCT).

For the assessment of the present claim 7 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.